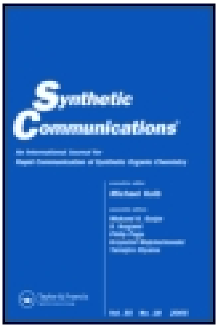

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An Efficient Synthesis of Anilinobenzylphosphonates

Hyun-Joon Ha [a] & Gong-Sil Nam [b]

[a] Department of Chemistry, Hankuk University of Foreign Studies Imun-Dong, Seoul, 130-791, Korea

[b] Division of Chemistry, Korea Institute of Science and Technology, P.O. Box 131 Cheongryang, Seoul, 130-650, Korea

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AN EFFICIENT SYNTHESIS OF ANILINOBENZYLPHOSPHONATES

Hyun-Joon Ha*, and Gong-Sil Nam
Department of Chemistry, Hankuk University of Foreign Studies, Imun-Dong
Seoul, 130-791 Korea, and Division of Chemistry, Korea Institute of Science and
Technology, P.O. Box 131 Cheongryang, Seoul, 130-650 Korea

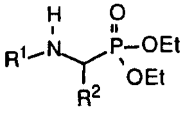
Abstract : An efficient one-pot synthesis of anilinobenzylphosphonates was achieved from the reaction of aniline, benzaldehyde, and dialkylphosphite in the presence of $BF_3 \cdot OEt_2$ as a catalyst.

Aminomethylphosphonates attracts attentions due to their synthetic and biological perspectives.[1,2]

$R^1{-}NH_2$ **1**

$R^2{-}CHO$ **2**

$R^1N{=}CHR^2$ **3**



4

A general synthetic method for aminomethylphosphonates (**4**) is addition of phosphorus to imines (**3**) as trialkylphosphites or dialkylphosphites. One of the

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*To whom correspondence to this author at the Hankuk University of Foreign Studies simplest imine, methyleneimine (R^2=H) is not stable enough to be isolated. Therefore, it should be generated *in situ* from N-(methoxymethyl)amines and/or hexahydro-1,3,5-triazines and reacted with trialkylphosphites to yield corresponding dialkylphosphontes in good yield.[3,4] When R^2 is alkyl or aryl imines are stable enough to be isolated. Their reactions with phosphites is studied quite well.[5] However, when both of R^1 and R^2 are aryl the synthesis of anilinobenzylphosphonates (4) is not known in the literature. We report herein an efficient one-pot synthesis of anilinobenzylphosphonates. The advantage of this synthetic method is use of $BF_3 \cdot OEt_2$ as a catalyst. Generation of imines[6] and addition of dialkylphosphites[7] were greatly accelerated by addition of $BF_3 \cdot OEt_2$ to give corresponding anilinobenzylphosphonates in high yield within 3 hrs.[8] This procedure has been proved to be good with diverse substituents on benzene ring of R^1 and R^2. **(Table 1)**

Table 1. Anilinobenzylphosphonates (4) prepared from the one-pot reaction of anilines, benzaldehyde and diethylphosphites in the presence of $BF_3 \cdot OEt_2$.

	Product		Yield[a]		Product		Yield[a]
	R^1=Ar	R^2=Ar	(%)		R^1=Ar	R^2=Ar	(%)
4a	Ph	Ph	64	**4g**	2,6-$(CH_3)_2$	Ph	97
4b	Ph	4-OH	50	**4h**	4-OCH_3	Ph	73
4c	Ph	4-OCH_3	40	**4i**	2-NO_2	Ph	73
4d	Ph	2-Cl	75	**4j**	2,3-Cl_2	Ph	84
4e	Ph	3-NO_2	42	**4k**	2,3,4-Cl_3	3-Cl	97
4f	3-CH_3	Ph	88				

a. Yield of pure isolated crystalline product except **4b**, not optimized.

Table 2. Physical properties of diethyl anilinobenzylphosphonates **4a-4k**

Product 4a-4k	mp[a] (ºC)	Molecular Formula[b]	IR(KBr) N-H, P=O, P-O-C (cm^{-1})	^{1}H NMR(CDCl$_3$/TMS) d, J(Hz)
4a	90-92	$C_{17}H_{22}NO_3P$	3272, 1237, 1056, 1019	1.05 (t, J=7, 3H); 1.25 (t, J=7, 3H); 3.82 (dq, J=7, J=7, 2H); 4.06 (dq, J=7, J=7, 2H); 4.73 (d, J=24, 1H); 6.45-7.6(m, 10H)
4b		$C_{17}H_{22}NO_4P$	3307, 1219, 1055, 1018	1.06 (t, J=7, 3H); 1.17 (t, J=7, 3H); 3.75 (dq, J=7, J=7, 2H); 4.06 (dq, J=7, J=7, 2H); 4.75 (d, J=24, 1H); 6.50-7.46(m, 9H)
4c	99-101	$C_{18}H_{24}NO_4P$	3297, 1239, 1048, 1023	1.10 (t, J=7, 3H); 1.23 (t, J=7, 3H); 3.70 (s, 3H); 3.90 (dq, J=7, J=7, 2H); 4.06 (dq, J=7, J=7, 2H); 4.73 (d, J=24, 1H); 4.93 (bs, 1H); 6.45-7.63 (m, 9H)
4d	104-105	$C_{17}H_{21}ClNO_3P$	3298, 1235, 1063, 1015	1.03 (t, J=7, 3H); 1.30 (t, J=7, 3H); 3.83 (dq, J=7,J=7, 2H); 4.22 (dq, J=7, J=7, 2H); 4.70 (bs, 1H); 5.30 (d, J=24, 1H); 6.5-7.8(m, 9H)
4e	87-89	$C_{17}H_{21}N_2O_5P$	3289, 1234, 1049, 1018	1.15 (t, J=7, 3H); 1.23 (t, J=7, 3H); 4.00 (dq, J=7,J=7, 2H); 4.16 (dq, J=7, J=7, 2H); 4.81 (bs, 1H); 4.90 (d, J=24, 1H); 6.46-8.50(m, 9H)
4f	125-129	$C_{18}H_{24}NO_3P$	3298, 1237, 1054, 1023	1.12 (t, J=7, 3H); 1.30 (t, J=7, 3H); 2.20 (s, 3H); 3.65 (dq, J=7, J=7, 2H); 4.14 (dq, J=7, J=7, 2H); 4.81 (d, J=24, 1H); 6.36-7.64(m, 9H)

(continued)

Table 2 Continued

4g	64-66	$C_{19}H_{26}NO_3P$	3391, 1251, 1050, 1019	0.97 (t, J=7, 3H); 1.17 (t, J=7, 3H); 2.13 (s, 6H); 3.78 (dq, J=7, J=7, 2H); 4.04 (dq, J=7, J=7, 2H); 4.46 (d, J=24, 1H); 4.73 (bs, 1H); 6.65-7.56(m, 8H)
4h	80-82	$C_{18}H_{24}NO_4P$	3368, 1233, 1049, 1017	1.06(t, J=7, 3H); 1.23 (t, J=7, 3H); 3.60 (s, 3H); 4.13 (dq, J=7, J=7, 2H); 4.90 (d, J=24, 1H); 4.91 (dq, J=7, J=7, 2H); 6.73 (s, 5H); 7.16-7.76(m, 4H)
4i	114-118	$C_{17}H_{21}N_2O_5P$	3368, 1233, 1055, 1017	1.11 (t, J=7, 3H); 1.20 (t, J=7, 3H); 4.30 (dq, J=7, J=7, 2H); 4.33 (dq, J=7, J=7, 2H); 5.30 (d, J=24, 1H); 6.51-7.6(m, 9H)
4j	64-68	$C_{17}H_{20}Cl_2NO_3P$	3403, 1244, 1055, 1018	1.13 (t, J=7, 3H); 1.23 (t, J=7, 3H); 3.83 (dq, J=7,J=7, 2H); 4.06 (dq, J=7, J=7, 2H); 4.86 (d, J=24, 1H); 5.90 (bs, 1H); 6.65-7.56 (m, 8H)
4k	112-115	$C_{17}H_{18}Cl_4NO_3P$	3396, 1245, 1049, 1024	1.17(t, J=7, 3H); 1.26 (t, J=7, 3H); 3.83 (dq, J=7, J=7, 2H); 4.12 (dq, J=7, J=7, 2H); 4.85 (d, J=24, 1H); 5.76(bs,1H); 6.30 (d, J=8, 1H); 7.03 (d, J=8, 1H); 7.10-7.52(m, 4H)

a. not corrected. b. satisfactory microanalyses obtained.

Typical reaction procedure is as follows. To a stirred solution of benzaldehyde (0.03 mol) and aniline (0.03 mol) in benzene was added $BF_3 \cdot OEt_2$ (0.03 mol). The reaction mixture was refluxed and the water generated was removed by means of a Dean-Stark trap. After being observed that all starting material was consumed on TLC the reaction mixture was cooled to room temperature. Diethylphosphite (0.03 mol) was added and the resulting mixture was refluxed. After the reaction was completed the solvent was removed by evaporation under reduced pressure, and the residual oil was recrystallized from ethylether. Results and physical properties of products are summarized in the **Table 1** and **2**.

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7. Addition of trialkylphosphites to imines with $BF_3 \cdot OEt_2$ as a catalyst was known. see, Birum, G. A., J. Org. Chem., 1974, 39, 209; Huber, J. W. and Gilmore, W. F. Tetrahdron Lett., 1979, 20, 1567

8. In the absence of $BF_3 \cdot OEt_2$ the reaction for **4a** through imine formation and addition of diethylphosphite takes more than 24 hrs.

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